REMARKS

Reconsideration of the captioned application as amended herewith is respectfully requested.

A petition for a one (1) month extension of time to file this Amendment is attached herewith.

The Office Action acknowledged Applicant's election with traverse of Group I but finalized the restriction requirement; objected to the specification under 35 USC §112, first paragraph; rejected claims 23 – 26 under 35 USC §112, first paragraph; rejected claims 1 – 2 and 23 – 26 under 35 USC §102(a) as being anticipated by Taylor et al.; and rejected claims 1 – 19 and 23 – 26 under 35 USC §103(a) as being unpatentable over Taylor et al., United States Patent No. 5,807,834 ("Morehouse"), Sun et al., 104 CA:147555 (1985) ("Sun"), and Pick et al., 91 CA:13847 (1979) ("Pick"). Claims 1 – 24 are pending in the application, with claims 20 – 22 being withdrawn from consideration.

This Amendment is filed concurrently with a Supplemental Information Disclosure Statement ("IDS") and a Declaration under 37 CFR §1.131.

Amendments to the Claims

Applicants have cancelled claims 25 and 26 without prejudice or disclaimer to the subject matter contained therein.

Applicants wish to correct the inadvertent typographical error made in claims 4 and 13, i.e., the term, "filtrates" should read "fibrates." Support for this amendment may be found in the Specifciation as originally filed at, for example, page 4, lines 24 – 25, and as such the amendment does not introduce new matter into the application.

The Objection to the Specification Under 35 USC §112, First Paragraph Has Been Overcome

The Office Action objected to the Specification under 35 U.S.C. §112, first paragraph, as "failing to adequately teach how to make and/or use the invention, and thereby failing to provide an enabling disclosure." Applicants respectfully disagree for the reasons that follow.

A. Antioxidants and Fibrates

According to the Office Action, the Specification allegedly fails to "set forth the criteria that defines antioxidants or [fibrates] useful in treating coronary disease." Applicants respectfully disagree.

As clearly set forth in the Specification, the fibrates suitable for use in the present invention include those known in the art as being cholesterol lowering agents. See Specification, page 4, lines 24 – 25. Applicants respectfully submit that one skilled in the art who was desiring such a fibrate cholesterol lowering agent would readily look to the literature, such as the Physician's Desk Reference ("PDR"), in order to select such a fibrate. Page 208 from the PDR, (55th Ed. 2001), a copy of which is included with the IDS filed concurrently herewith, explicitly shows examples of such suitable fibrates.

Similarly, Applicants respectfully submit that one skilled in the art who was desiring a antioxidant suitable for treating coronary disease would also readily look to the literature, such as the New England Journal of Medicine ("Journal"), in order to select such an antioxidant. For example, the article, Diaz, et al., "Antioxidants and Atherosclerotic Heart Disease," from the Journal (August 7, 1997), and the article, Duffy, et al., "Antioxidants and Endothelial Function," Heart Failure, 135 – 163 (Summer/Fall 1999), explicitly show examples of such suitable antioxidants. Copies of these articles are also included in the IDS filed herewith. Moreover, Applicants expressly list exemplary antioxidants, such as, for example, vitamin E and vitamin C, in the Specification as being suitable for use with the present invention. See Specification, page 4, lines 28 – 29.

When considering enablement, one skilled in the art is assumed to know what is available in the art. Thus, the test of enablement is whether one skilled in the art could make or use the invention based upon the disclosures in the patent coupled with information known in the art, without undue experimentation. See United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1998). A patent specification does not need to teach, and preferably omits, that which is well-known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986).

Therefore, Applicants respectfully submit that both the disclosure in the Specification as well as the knowledge already in the prior art would provide sufficient enablement for one skilled in the art to select a suitable fibrate and a suitable antioxidant for use in the present invention.

B. Treatment Regimens of Prevention or Regression of Arteriosclerosis

According to the Office Action, the Specification allegedly fails to "provide information allowing the skilled artisan to ascertain [the treatment regimens for arteriosclerosis prevention] without undue experimentation." Applicants respectfully disagree.

As set forth in the Specification as originally filed on page 3, lines 9 – 10, the term "prevention," as used herein, "is meant to proactively stop the development of arteriosclerotic lesions, e.g. fatty streaks." Applicants respectfully submit that this situation is clearly set forth in the Examples.

More specifically, Example 1 set forth on pages 7 – 9 of the Specification describes an experiment wherein 23 rabbits having no fatty streak formation were fed chow supplemented with 1% cholesterol. This experimental system has been used previously for the evaluation of the efficacy of pharmaceutical compounds for preventing artherosclerosis. See Specification, page 7, line 32 – page 8, line 5. In this experiment, twelve of the rabbits consumed water containing acetaminophen ("APAP"), while the other eleven rabbits remained on regular water for the remainder of the study. The 40 mg/kg dose of APAP given to each 2.5 kg rabbit is equivalent to about a 2800 mg/day dose in a 70 kg human. See Specification, page 8, lines 15 – 16. After 12 weeks, the aorta of each rabbit was examined for fatty streak deposits. The results showed that the rabbits that consumed APAP had significantly reduced aortic fatty streak areas, which is well known as an initial sign of atherosclerosis. Thus, the administration of APAP in accordance with this regimen precluded the development and progression of fatty streak development.

Applicants respectfully submit that, based upon the disclosure of this experiment in the Specification, the skilled artisan would have sufficient information to ascertain the treatment regimens for arteriosclerosis prevention without undue experimentation. Thus, Applicants further respectfully submit that the objection to the Specification under 35 U.S.C. §112, first paragraph, has been overcome and should be withdrawn.

The Rejection of Claims 23 - 26 Under 35 USC §112, First Paragraph Has Been Overcome

Claims 23 - 26 stand rejected under 35 U.S.C. §112, first paragraph. In view of the cancellation of claims 25 and 26, and the arguments set forth above, Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

The Rejection of Claims 1 – 2 and 23 - 26 Under 35 USC §102(b) Over Taylor, et al. Has Been Overcome

Claims 1 – 2 and 23 – 26 stand rejected under 35 U.S.C. §102(b) as being anticipated by Taylor, et al. Applicants disagree for the reasons set forth below.

Taylor, et al. is an abstract that was published on 2 November 1999, which is less than one (1) year before Applicant's United States priority filing date of 3 August 2000.

Applicants enclose herewith a declaration under 37 CFR 1.131 ("Declaration"), which demonstrates that Applicants had conceived and reduced to practice the claimed invention before November, 1999. In view of the attached Declaration, Applicant respectfully submits that the rejection of claims 1 – 2 and 23 – 26 under 35 U.S.C. §102(b) based on Taylor, et al. has been overcome and should be withdrawn.

The Rejection of Claims 1 – 19 and 23 - 26 Under 35 USC §103 Over Taylor, et al., Morehouse, Pick, and Sun Has Been Overcome

Claims 1 – 19 and 23 – 26 stand rejected under 35 U.S.C. §103 as being unpatentable by Taylor, et al., Morehouse, Pick, and Sun. Applicants disagree for the reasons set forth below.

In view of the attached Declaration and the arguments set forth above, Applicant respectfully submits that the rejection of claims 1 – 19 and 23 – 26 under 35 U.S.C. §103 based on Taylor, et al. has been overcome and should be withdrawn.

Morehouse discloses compositions, such as atorvastatin, that are useful in the treatment of atherosclerosis. However, Morehouse neither discloses nor suggests the use of APAP as a primary agent for treating arteriosclerosis, let alone the combination of APAP with a secondary agent for treating arteriosclerosis.

Sun discloses that vitamin C and vitamin E "decreased the incidence of arteriosclerosis induced by cholesterol." However, Sun neither discloses nor suggests the use of APAP as a primary agent for treating arteriosclerosis, let alone the combination of APAP with a secondary agent for treating arteriosclerosis.

Pick discloses the use of aspirin in exerting "a protective effect in the primary prevention of diet-induced coronary atherosclerosis." However, Sun neither discloses nor suggests the use of APAP as a primary agent for treating arteriosclerosis, let alone the combination of APAP with a secondary agent for treating arteriosclerosis.

Therefore in view of the above, Applicants respectfully submit that the rejection of claims 1 – 19 and 23 – 26 under 35 USC §103(a) has been overcome and should be withdrawn.

Conclusion

It is submitted that the foregoing amendments and remarks place the case in condition for allowance. A notice to that effect is earnestly solicited.

Respectfully submitted,
Nelson, et al.

By: _____
Michele G. Mangini
(Attorney for Applicants)
Reg. No. 36,806
Dated: May 20, 2003

Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003
(732) 524-2810

Att.
IDS w/ 3 references
Rule 131 Declaration w/ Appendices A - C
One Month Extension of Time

Docket No. MCP 267

#10
4DP

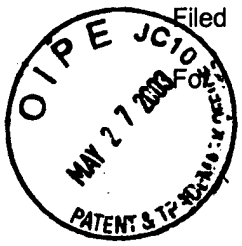
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Nelson, et al.

Serial No. : 09/887,465 Art Unit: 1617

Filed : 22 June 2001 Examiner: Travers, Russell

For : USE OF ACETAMINOPHEN TO PREVENT AND TREAT ARTERIOSCLEROSIS



I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on

May 22 2003
(Date of Deposit)

Michele G. Mangini
(Name of applicant, assignee, or Registered Representative

(Signature)

May 22 2003
(Date of Signature)

Assistant Commissioner For Patents
Washington, D.C. 20231

DECLARATION UNDER 37 CFR 1.131

Dear Sir:

1. This Declaration is submitted to establish conception and reduction to practice of the invention in the above-identified application in the United States at a date prior to 2 November 1999. It is my information and belief that the referenced entitled, "Acetaminophen Inhibits Fatty Streak Formulation and LDL Oxysterols in Hypercholesterolemic Rabbits, " by Taylor, et al., 100 Circulation p. I-697, Abstract No 3677 (Supp. 18) was published on 2 November 1999 (hereinafter "Taylor Abstract"). A copy of the Taylor Abstract is attached hereto as Exhibit A. The Taylor Abstract was cited in the Office Action mailed on 27 January 2003 in the above-referenced application.

3. I, Edward B. Nelson, MD, PhD, am one of the inventors of the invention described and claimed in the above-identified application.

4. I am presently in the employ of McNEIL Consumer & Specialty Pharmaceuticals Division of McNEIL-PPC, Inc., located at 7050 Camp Hill Road, Fort Washington, PA 19034, as Vice President, Scientific Affairs. This division is a successor to McNEIL Consumer Healthcare, a division of McNEIL-PPC, Inc. At and before the completion of the invention, I was in the employ of McNEIL Consumer Healthcare, a division of McNEIL-PPC, Inc., as Vice President, Medical/R&D. For purposes of this Declaration, these divisions shall be referred to as "McNEIL."

5. I understand that the claims of the present invention have been rejected in view of the Taylor Abstract.

6. Appended hereto as Exhibit B is a true copy of the Clinical Study Agreement between McNEIL and Baylor College of Medicine ("Baylor"), which I executed on behalf of McNEIL (hereinafter "Agreement"). The protocol entitled "Effect of Acetaminophen on the Development of Atherosclerosis and on the Response to Vascular Injury in the Hypercholesterolic Rabbit Model" ("Protocol") was developed by myself in conjunction with Dr. Addison Taylor, and was performed by Baylor at my request pursuant to the terms of the Agreement. A copy of the Protocol is attached to the Agreement.

7. Appended hereto as Exhibit C is a true copy of the American Heart Association publication submission form ("Submission Form"), to which was attached a copy of the data published in the Taylor Abstract ("Data"). The Data reflected the results of the study performed in accordance with the Protocol. As required by Section 4(c) of the Agreement, Baylor provided me with a copy of the Data to review in advance of Baylor's submitting that Data for publication. This memorializes the conception and reduction to practice of the claimed invention.

8. In particular, on page 3 of the Protocol and in the Data attached to the Submission Form, it can be seen that the invention of this application, i.e. a method for treating atherosclerosis, was conceived and reduced to practice prior to 2 November 1999, which is earlier than the 35 USC §102(a) date of the Taylor Abstract.

9. All dates that have been redacted in the Exhibit are before 2 November 1999.

10. I, Edward B. Nelson, further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further declare that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 35 USC §1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or patent issuing thereon.

By: Edward B Nelson
Edward B. Nelson, MD, PhD

Country of Citizenship: USA

Address: 3 Wayne Circle, Lower Gwynedd, Pa, 19002
Date: May 21,2003

Att.
Appendix A: Taylor Abstract
Appendix B: Clinical Study Agreement with Protocol
Appendix C: Submission Form with Data
Mcp267-131decn.doc

Appendix A

Acetaminophen Inhibits Fatty Streak Formation and LDL Oxo-sterols in Hypercholesterolemic Rabbits

A A Taylor, J R Raya, L. R. Rog rs, and C V Smith, D pts of M dicine and Pediatrics, Baylor Coll g of M dicin , Houston, TX 77030

Acetaminophen (A), a widely used analgesic, inhibits oxidation of LDL in humans. METHODS: We examined the antioxidant and anti-atherosclerotic properties of A in rabbits with dietary hypercholesterolemia produced by feeding rabbits chow with 1% cholesterol daily for 12 weeks. One group received A via their drinking water at doses comparable to those used in humans (100 mg/day) and controls (C) did not. Blood was obtained every 4 weeks for lipid analyses and to assess liver and kidney function. At sacrifice blood was collected for isolation of LDL and routine serum chemistry measurements, the aorta from ascending arch to the iliac bifurcation was removed, open longitudinally, photographed under blue filtered light, and the total and fatty streak areas determined by planimetry. Oxo-sterol concentrations in LDL were determined by FID-gas chromatography. Conjugated dienes (TBARS) during 24-hr Cu^{++}-O_2 oxidation of LDL were determined by spectrophotometry. RESULTS: The fatty streak/total aortic area ratio in 12 A compared to 11 C rabbits (0.32 + 0.05 vs 0.58 + 0.06) was significantly reduced ($p<0.001$) although there were no significant differences in circulating total plasma cholesterol levels in the two groups (1592±43 mg/dl A vs 1441±87 mg/dl C). TBARS formed during LDL oxidation were similar in the two groups. LDL concentrations of oxo-sterols from A and C are compared in the following table. All values are in nmol/mg LDL.

	7aOH-Cholesterol	7bOH-Cholesterol	7keto-Cholesterol	5a,6a-epoxide	5b,6b-epoxide
A	0.58+0.12	0.32+0.07	0.41+0.14	0.11+0.05	0.12+0.13
C	2.31+0.62	1.01+0.26	3.86+1.72	0.49+0.08	0.24+0.05

CONCLUSIONS: These findings suggest that A in doses therapeutically relevant to man has antiatherosclerotic properties in hypercholesterolemic rabbits, perhaps by its inhibitory effect on the formation of highly atherogenic oxo-sterols in LDL.

Baylor Appendix B

COPY

CLINICAL STUDY AGREEMENT

This Agreement by and between McNeil Consumer Products Company ("Sponsor"), a Pennsylvania corporation, with offices at 7050 Camp Hill Road, Fort Washington, Pennsylvania 19034, and Baylor College of Medicine, ("Institution") located at One Baylor Plaza, Houston, Texas 77030 is made this

Background

Whereas Sponsor has requested Institution and its employees, to conduct a clinical study according to Protocol entitled: "Effect of acetaminophen on the development of atherosclerosis and on the response to vascular injury in the hypercholesterolemic rabbit model", attached hereto as Exhibit A and incorporated herein by reference (the "Study"); and

Whereas Institution and Principal Investigator, Addison A. Taylor, M.D., Ph.D., are equipped to undertake the Study and have agreed to perform the Study on the terms and conditions hereinafter set forth;

Now, therefore, in consideration of the premises and the mutual promises and covenants expressed herein, the parties agree as follows:

1. Performance of Study: Institution and Principal Investigator agree to use their best efforts and professional expertise to perform the study in accordance with the Protocol. In the event that the Principal Investigator becomes no longer affiliated with the Institution, the Institution shall provide written notice to Sponsor within three(3) days of such departure. Sponsor shall have the right to approve any new Principal Investigator designated by Institution. The new Principal Investigator shall be required to agree to the terms and conditions of this Agreement. Sponsor may decide, however, to continue the Study only with the original Principal Investigator, in which case Institution shall take all necessary steps to accommodate Sponsor's decision. Principal Investigator shall not make use of Study Drug other than for the performance of the Study and shall return to Sponsor any unused Study Drug at the earlier of the conclusion of the Study or termination of this Agreement.

2. Terms and Termination: Copied for legal

a) Term. The term of this Agreement shall begin on the date first mentioned and end on unless sooner terminated in accordance with the terms hereof. The parties contemplate that the term may be extended by mutual agreement if events beyond the parties' control delay completion of the Study beyond the expiration date.

b) Termination. The Study may be terminated by Sponsor at any time in the exercise of its sole discretion upon fifteen (15) days prior written notice to Principal Investigator. Reasons for Study termination may include but are not limited to: (a) breach of contract; (b) receipt of safety information that makes it prudent to do so; or (c) receipt of data suggesting lack of sufficient efficacy. Notwithstanding the above, Sponsor may immediately terminate the Study if, with its sole

judgment, such immediate termination is necessary based upon considerations of subject safety. Upon receipt of notice, Principal Investigator agrees to promptly terminate conduct of the Study to the extent medically permissible for any subjects. In the event of termination hereunder, other than as a result of a material breach by Principal Investigator, the total sums payable by Sponsor pursuant to this Agreement shall be equitably pro rated for actual work performed to the date of termination with any unexpended funds previously paid by Sponsor to Institution being refunded to Sponsor.

3. Institutional Review Boards ("IRB")/Informed Consent:

a) IRB. Institution and Principal Investigator shall be responsible for maintaining approval of the Protocol, Informed Consent and Study advertisement, if any, from the appropriate IRB during the Study. In the event the IRB requires changes in the Protocol or Informed Consent, such changes shall not be implemented until Sponsor is notified and gives its approval. The Protocol and the Informed Consent shall not be revised without the prior written agreement of Sponsor and the IRB.

b) Informed Consent. Institution and Principal Investigator shall be responsible for obtaining an Informed Consent document signed by or on behalf of each human subject, and otherwise in accordance with applicable FDA regulations which Informed Consent document shall be the document approved by the Sponsor and the IRB, prior to the subject's participation in the Study.

4. Ownership of Data, Confidentiality and Publication:

a) Ownership. All case report forms and other data (including without limitation, written, printed, graphic, video and audio material, and information contained in any computer data base or computer readable form) generated by the Institution and Principal Investigator in the course of conducting the Study (the "Data") shall be the property of Sponsor, which may utilize the Data in any way it deems appropriate. Any copyrightable work created in connection with performance of the Study and contained in the Data shall be considered a work made for hire, whether published or unpublished and all rights therein shall be the property of Sponsor as employer, author and owner of copyright in such work.

b) Confidentiality. All information concerning name of drug, and covering Sponsor's operations, including but not limited to Sponsor's patent application, formulas, manufacturing processes, basic scientific data, prior clinical data and formulati n information supplied by Sponsor to the Principal Investigator and not previously published are considered confidential and shall remain the sole property of Sponsor. Both during and after the term of this Agreement, Institution and Principal Investigator will use diligent efforts to maintain in confidence and use only for the purposes contemplated in this Agreement (i)

information which is identified in the preceding sentence as confidential or which a reasonable person would conclude is the confidential and proprietary property of Sponsor and which is disclosed by or on behalf of Sponsor to Institution and Principal Investigator, and (ii) Data which is generated as a result of this Study. The preceding obligations shall not apply to Data or information (i) which has been published through no fault of Institution and Principal Investigator, (ii) which Sponsor agrees in writing may be used or disclosed, or (iii) which is published in accordance with paragraph C of this Article. The provisions in this paragraph shall survive the termination or expiration of this Agreement.

c) Publication Sponsor will have the right to review any paper for publication, including oral presentations and abstracts, which utilizes data generated from the Study to be conducted by the Principle Investigator and the Institution. It is agreed that all publications directly related to the Study shall be co-authored by one or more individuals of Sponsor. Before any such paper, presentation or abstract is presented or submitted for publication, a complete copy will be given to Sponsor at least ninety (90) days prior to submission to any third party. Sponsor will review any such paper and give its comments to the author or Institution promptly. No paper which incorporates Sponsor's Confidential Information will be submitted for publication without Sponsor's prior written consent. All publications will identify Sponsor as the manufacturer of the Study Drug in the publication. The Institution and/or author will comply with Sponsor's further request to delete references to Sponsor's Confidential Information in any such paper and will withhold publication of the same, an additional ninety (90) days from the date Sponsor provides Institution with notice in order to permit Sponsor to obtain patent protection if Sponsor deems it necessary.

5. Patents: All rights to any discovery or invention conceived or conceived and reduced to practice in the direct performance of the work conducted under this Agreement in accordance with the Protocol shall belong to Sponsor. Institution and Principal Investigator agree to assign to Sponsor, at the request of Sponsor, the sole and exclusive ownership thereto, upon the payment of costs by Sponsor, if any, incurred by Institution and Principal Investigator in the filing, prosecution, or maintenance of any patent application or patent issuing thereon. Such application, if any, shall be filed and prosecuted by Sponsor. Institution and Principal Investigator shall promptly disclose to Sponsor any invention or discovery arising under this Agreement.

6. Reporting of Data: Institution and Principal Investigator agree to provide Sponsor periodically and in a timely manner during the term of this Agreement with th data called for in the Protoc l on properly completed case rep rt forms. Cas report forms shall b submitted pursuant to the schedule provided in Exhibit B. Institution and Principal Investigator als agre to notify Spons r within twenty-four (24) hours after learning of any serious and/or unexpected adverse drug experienc (as defined in the Protocol) affecting any patient in the Study. Institution and Principal

Investigator further agree to follow up such notification with appropriate reports in compliance with all applicable legal and regulatory requirements.

7. Compliance with Applicable Laws: Institution and Principal Investigator agree to conduct the Study and maintain records and data during and after the term of this Agreement in compliance with all applicable legal and regulatory requirements, including without limitation, any applicable requirements of the United States Food and Drug Administration ("FDA") and the Federal Drug Enforcement Administration ("DEA"). Institution and Principal Investigator shall not employ, contract with or retain any person directly or indirectly to perform services under this Agreement if such person is debarred by FDA under 21 U.S. C. 335a. Upon written request from Sponsor, Institution and Principal Investigator shall within ten (10) days, provide written confirmation that it has complied with the foregoing obligation.

8. Project Management: Sponsor and Institution will each designate an individual for the Study who has overall authority to control and direct the services requested by McNeil or performed by the Institution. This point of contact will coordinate communication between individuals in their respective organizations.

Studies shall be reported on a monthly basis, with status reports outlining technical completion of tasks as well as a detailed evaluation of study expenditures. Institution's Senior Management will be available as needed to ensure satisfactory completion of the Study.

9. Monitoring of Study:

a) Inspections/Audits. During the term of this Agreement, Institution and Principal Investigator agree to permit representatives of Sponsor and/or the FDA to examine at any reasonable time during normal business hours (i) the facilities where the study is being conducted, (ii) raw study data including original patient records, and (iii) any other relevant information necessary to confirm that the Study is being conducted in conformance with the Protocol and in compliance with applicable FDA and DEA laws and regulations. Institution and Principal Investigator shall immediately notify Sponsor if FDA or DEA schedules or, without scheduling, begins an inspection and shall promptly, upon issuance, provide Sponsor a copy of any FDA or DEA correspondence resulting from any such inspection.

b) Corrective Action. Institution and Principal Investigator agree to take any reasonable actions requested by Sponsor to cure deficiencies noted during an audit or inspection. In addition, Sponsor shall approv any correspondence to FDA or DEA generated as a result of an FDA or DEA inspection prior to submission by Institution and Principal Investigator.

10. Publicity: None of the parties shall use the name of any other party for promotional purposes without th prior written consent of the party whos nam is proposed to be used, nor shall either party disclose th existence or substance of this Agreement except as required by law.

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11. Advertising: Sponsor shall provide sponsor-approved advertising to the Institution and Principal Investigator to be us d to recruit subjects to participate in the Study. Institution and Principal Investigator shall obtain Institutional Review Board approval prior to the first use of this advertising. Institution and Principal Investigator shall only use such approved advertising for the purpose of subject recruitment.

12. Independent Contractor: Institution and Principal Investigator are acting in the capacity of independent contractor hereunder and not as employee or agent of Sponsor, except as set forth in Article 4(a) hereof.

13. Compensation: The budget and compensation to be paid for the Study is contained in Exhibit B and Exhibit C. Payment shall be due and payable in accordance with the schedule set forth in Exhibit B.

14. Controlling Law: This Agreement shall be governed by and construed in accordance with the laws of the Commonwealth of Pennsylvania without regard to its conflicts of laws provisions.

15. Indemnification:

a) Spons[redacted]nd, indemnify and hold harmless Institution and any of [redacted]or employees from any and all losses, costs, expenses, [redacted]aims, actions and damages, based on a personal injury to [redacted] directly caused by using the Study Drug during the course of [redacted]tudy.

b) The above obligation of Sponsor shall not apply and Sponsor shall not be liable and in fact Institution and Principal Investigator shall be liable ~~and shall indemnify Sponsor~~ for actions or claims in any way arising from or caused by the willful, reckless, or negligent acts or omissions, or profe[redacted]nal malpractice of the Institution or any of their agents or emplo[redacted] arising from or caused by any failure to comply with the[redacted], with Sponsor's written recommendations and i[redacted] relative to the use of the Study Drug, or with any [redacted]n FDA or other governmental requirements or law.

Sponsor

c) [redacted]obligation of the ~~Indemnifying Party~~ to defend, indemnify and hold [redacted]rmless shall apply only if the ~~Indemnified Party~~ properly notifies the ~~Indemnifying Party~~ upon receipt of notice of any claim or suit, permits the ~~Indemnifying Party~~ and its attorneys and personnel, at ~~Indemnifying Party's~~ discretion and cost, to handle and control the defense of such claims or suits, including pretrial, trial or settlement, and the ~~Indemnifying Party~~ and its attorneys in such defense. Th ~~Indemnified Party~~ further agrees that he/she will not settle or compromis any such claim or suit without the prior written consent of ~~Indemnifying Party~~. Institution

16. Insurance: Institution and Principal Investigator shall secure and maintain in full force and effect through the performance of the Study (and following termination of the Study to cover any claims arising from the Study)

insurance coverage in amounts appropriate to the conduct of Institution and Principal Investigator business activities and the services contemplated by the Study.

17. Agreement Modifications: This Agreement may not be altered, amended or modified except by written document signed by all parties.

18. Notice: Any notices given hereunder shall be deposited in the United States mail, sent by facsimile or personally delivered as follows:

TO: McNeil Consumer Products Company
Camp Hill Road
Fort Washington, PA 19034
Attention: Edward B. Nelson, M.D., Ph.D.

TO: Baylor College of Medicine
One Baylor Place
Room 802E
Houston, TX 77030
Attn: Carol Howell

19. Arbitration: Any controversy or claim arising out of or relating to this Agreement, or the parties' decision to enter into this Agreement, or the breach thereof, shall be settled by arbitration in accordance with the Commercial Arbitration Rules of the American Arbitration Association, and judgment upon the award rendered by the arbitrator(s) may be entered in any court having jurisdiction thereof. The arbitration shall be held in Pennsylvania, and as provided in section "Controlling Law", shall apply the substantive law of Pennsylvania, except that the interpretation and enforcement of this arbitration provision shall be governed by the Federal Arbitration Act. The arbitrator(s) shall not award either party punitive damages and the parties shall be deemed to have waived any right to such damages. Further, the arbitrator(s) shall be bound by the express terms of this Agreement .

20. Conflict with Protocol: If any of the provisions of this Agreement conflict with any provision of the Study Protocol, this Agreement shall take precedence.

IN WITNESS WHEREOF, the parties hereto have caus[illegible]nt to be executed by their duly authorized representatives as of the da[illegible] written.

BY Edward B. Nelson

Edward B. Nelson, M.D., Ph.D.
Vice President, Medical and R&D
McNeil Consumer Products Company
Date:

BY

ROBERT R. ROCH, M.D.
VICE PRESIDENT AND DEAN OF RESE
Institution's Representative
Baylor College of Medicine
Date:

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EXHIBIT A

PROTOCOL:

Effect of acetaminophen n the dev l pment of ather scler sis and n the respons to vascular injury in the hypercholesterolemic rabbit model

Inv cor.

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Baylor College of Medicine
Center for Experimental Therapeutics

Proposal:

Effect of acetaminophen on the development of atherosclerosis and on the response to vascular injury in the hypercholesterolemic rabbit model

Investigators:

Addison A. Taylor, M.D., Ph.D.
Sarat Sundroyothen, MD
James L. Pool, MD

Background:

Considerable evidence has accumulated to suggest that oxidation reactions participate in the development of atherosclerosis in a variety of animal species, particularly the Watanabe genetic hyperlipidemic and the dietary hyperlipidemic rabbit. One hypothesis is that endothelial damage from any one of a variety of injurious stimuli results in "activation" of endothelial cells. These activated endothelial cells produce reactive oxygen species from the increased metabolism of membrane-bound arachidonic acid. Reactive oxygen, either directly through the activation of circulating leukocytes or through the stimulation of metabolic pathways leading to the formation of chemoattractant cytokines like MCP-1 and pro-inflammatory lipid-derived mediators like platelet activating factor, causes the adhesion of monocytes to the endothelium and their subsequent diapedesis into the underlying vascular smooth muscle layer where they engulf lipids and are ultimately converted into lipid-laden macrophages or foam cells. It has been postulated that activated leukocytes, particularly neutrophils and monocytes, both of which are capable of producing large quantities of reactive oxygen species, contribute to the oxidation of low-density lipoproteins (LDL) adjacent to these cells. The oxidized LDL rich in lysophosphatidylcholine that is produced by this mechanism is well known to interfere with the capacity of the endothelial cell to produce the potent vasodilator and inhibitor of both platelet and leukocyte adhesion and vascular smooth muscle cell growth and migration, nitric oxide.

Acetaminophen has been demonstrated to have antioxidant properties in several laboratories including our own. In vitro, acetaminophen or, less likely, one of its metabolites, can inhibit both chemically induced (copper-catalyzed oxygen) or cell (macrophage) mediated oxidation of LDL in a concentration-dependent manner. The possibility that acetaminophen can modify one or more of the biochemical steps that leads to the formation of atherosclerotic plaques in animals or man through this antioxidant effect has not been rigorously tested. There are theoretical reasons to believe that acetaminophen may also have beneficial effects on the exuberant vascular smooth muscle cell response to vascular wall endothelial injury that occurs with angioplasty since oxidative responses to this inflammatory injury are thought to decrease the release of

nitric oxide from the vascular endothelium and to negate the anti-platelet and growth/migration inhibiting properties of nitric oxide through mechanisms summarized above.

Objectives:

1. To determine if acetaminophen will decrease the rate of progression of atherosclerosis in the hyperlipidemic rabbit produced by high dietary cholesterol.
2. To determine if acetaminophen reduces the exaggerated vascular wall response (neointima formation) to balloon catheter injury in the dietary hypercholesterolemic rabbit.\

Study Protocol

Animal model

The New Zealand white rabbit will be used in these studies since it has been shown to develop extensive vascular fatty streak deposition in response to 1% dietary cholesterol. The total serum cholesterol of rabbits exposed to this diet increases from about 175 mg/dl to 1200-1500 mg/dl. Well defined fatty streaks that include oxidized lipoproteins and lipid-laden macrophages are clearly demonstrable in the walls of the arterial vasculature, especially the aorta, after 8 weeks of this diet and even more prominent after 12 weeks. Thus, all rabbits in this protocol will be exposed to a 1% cholesterol diet for at least 12 weeks before any histological characterization is initiated. Rabbits will initially be divided into two groups, those who receive acetaminophen dissolved in their tap water at a concentration of xx mg/ml. Initial concentrations will be based on the assumption that the average adult male rabbit weighing 3-4 kg consumes about 60 ml of water per day. The average daily volume of water consumed by each rabbit will be monitored every other day throughout the study. The concentration of acetaminophen in the drinking water will be adjusted to assure that each rabbit receives an oral dose of approximately 100 mg acetaminophen/day. Every 4 weeks rabbits will be placed temporarily in a restraining cage and 5 ml blood will be collected from an ear vein for measurement of serum lipids, electrolytes, renal and hepatic function. At the end of 12 weeks, rabbits will be divided into 4 groups, each of which will be evaluated or further studied as described below.

Group #	Description
1	Hypercholesterolemia – no acetaminophen
2	Hypercholesterolemia – acetaminophen
3	Hypercholesterolemia – no acetaminophen – carotid balloon catheter injury
4	Hypercholesterolemia – acetaminophen – carotid balloon catheter injury

Groups 1 and 2:

At the end of 12 weeks of high cholesterol diet, animals will be anesthetized with a cocktail containing ketamine, acepromazine and xylazine. The femoral artery will be catheterized, blood pressure measurements made via pressure transducer, and the animal exanguinated. In addition to blood for serum lipids, electrolytes, renal and hepatic function, as much as blood as possible will be collected for isolation of low density lipoproteins. The heart will be removed and weighed. The carotid arteries will be carefully removed and stored in oxygenated Krebs buffer for subsequent determination of endotheloium-dependent responses to acetylcholine and endothelium-independent responses to sodium nitroprusside of arterial rings in an organ chamber containing warmed, oxygenated Krebs solution. The entire length of the aorta from the aortic valve to the iliac bifurcation will be removed intact, opened longitudinally and pinned to a silastic petri dish so that it can be photographed under blue-filtered light for quantification of the extent of fatty streak formation. Using a newly established gradient elution HPLC technique recently established in the laboratory of Dr. Chow Yi Yang, we will separate and quantify the proportion of LDL in plasma that is native vs. that which is oxidized. HPLC fractions from each of these LDLs will be collected and the lipid hydroxy acid and hydroperoxide content of each will be determined by previously published techniques. Results obtained from animals in group 1 will be compared with those from group 2.

Segments of carotid arteries from hypercholesterolemic rabbits will be suspended in organ chambers containing warmed, oxygenated Krebs. The arteries will be passively stretched to their optimum length-tension relationship. After precontraction with phenylephrine (10-6M), arterial rings will be exposed to progressively higher concentrations of either acetylcholine (10-9 to 10-4 M) or sodium nitroprusside. After washing for 20-30 min., the alternate agent will be evaluated in the same rings. Area under the curve for the dose response curves and the calculated PD50 for each agent will be used to compare the results from groups 1 and 2.

Groups 3 and 4

After 12 weeks of a high cholesterol diet, the rabbits from groups 3 and 4 will undergo balloon catheter injury of one carotid artery as described previously. The contralateral carotid artery will serve as a control. During a 2 week period of recovery from the surgery, all animals will continue to receive a high cholesterol diet and acetaminophen in their drinking water if they are in group 4. At the end of the two week recovery period, the animals will be anesthetized as described above for groups 1 and 2, and blood, carotids, heart and aortas will be removed as described above. However, instead of assessing vasorelaxant responses to vasodilators, the carotid arteries will be fixed in paraformaldehyde, embedded in OTC, and representative sections made for quantification by planimetry of the extent of carotid artery neointima formation in the catheter injured carotid compared to the contralateral carotid. If a significant difference between neointima formation of acetaminophen-treated and –untreated rabbits is noted, additional immunohistochemical studies of leukocytes, adhesion molecule expression will be carried out.

Effect of Acetaminophen on Development of Atherosclerosis in Rabbits

Budget		Unit Cost	Units	Study Cost	Subtotals
Personnel					
Technician - animal			0.5		
Technician - laboratory			0.25		
Study Director			0.05		
Animal Costs					
Rabbit Purchase			50		
Rabbit Housing	120 d/rabbit		6000		
Rabbit Chow	1 bag/8 rabbits/90 d		8.333333		
Laboratory Supplies					
Organ Chambers			12		
Histology			12		
LDL chemistry			24		
			Total	Direct	
			BCM	Indirect	
			Total		

Appendix C

American Heart Association
ABSTRACT SUBMISSION FOR
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Title:

Acetaminophen Inhibits Fatty Streak Formation and LDL Oxysterols in Hypercholesterolemic Rabbits

Abstract:

Acetaminophen (A), a widely used analgesic, inhibits oxidation of LDL in humans. Methods: We examined the antioxidant and anti-atherosclerotic properties of A in rabbits with dietary hypercholesterolemia (fed daily for 12 weeks with chow containing 1% cholesterol). One group received A via the drinking water at doses comparable to those used in humans (100 mg/day) and controls (C) did not. At sacrifice blood was collected for measurements of lipids, renal and hepatic chemistries, and for isolation of LDL. The entire aorta was removed, opened longitudinally, photographed, and the total and fatty streak areas determined by planimetry. Oxysterols in isolated LDL were determined by FID-gas chromatography. Results: TBARS, determined by spectrophotometry during 24hr Cu^{++}-O_2 oxidation of LDL, were similar in A and C. The fatty streak/total aortic area ratio in 12 A compared to 11 C rabbits (0.32±0.05 vs 0.58±0.06) was markedly reduced ($p<0.001$) although there were no differences in circulating total plasma cholesterol levels (1592±43 vs 1441±87 mg/dl, A vs C). Circulating indices of renal and hepatic function were similar in the 2 groups. Concentrations of 5 oxysterols in nmol/mg LDL were all significantly lower in A vs C ($p<0.05$ - see table). Conclusions: These findings indicate that clinically relevant doses of A have anti-atherosclerotic properties in an hypercholesterolemic animal model, perhaps by its capacity to inhibit the formation of highly atherogenic oxysterols in LDL.

	7αOH-Cholesterol	7βOH-Cholesterol	7keto-Cholesterol	5α,6α-Epoxide	5β,6β-Epoxide
A	0.58±0.12	0.32±0.07	0.41±0.14	0.11±0.05	0.12±0.13
C	2.31±0.62	1.01±0.26	3.86±1.72	0.49±0.08	0.24±0.05